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Dementia Precox Studies

THE PRODUCTION OF TOXIC AMINES IN THE INTESTINAL TRACT.

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In our studies of dementia precox the observation of the intestinal tract with the barium meal and the fluoroscope has the greatest interest. By this means it has been learned that the normal stomach harbors the meal only from two to four hours. During this period the stomach is in regular peristaltic activity. The timer of this activity has been thought to rest in the contraction of the pylorus when the acid cud from the stomach is squirted violently into the alkaline duodenum. Depending upon the acidity of this cud, upon its quantity, or upon its mechanical irritability the reaction is prompt or slow.

There is also a "musculo-neural ligament" which connects the pylorus with the ileocecal and with the colonic sphincters. The activity of the ileocecal and colonic sphincters begins with the activity of the pylorus.

But for the cardiac sphincter, the stomach would empty itself into the esophagus at the beginning of peristalsis. The stomach and the cecum, or proximal colon, are each guarded by two sphincters. The cardiac sphincter is at the entrance of the stomach, the ileocecal sphincter is at the entrance of the cecum.

These sphincters only open to allow the two viscera they guard to receive the cud. They close at once and remain closed during the violent activity of peristalsis.

Just why the pylorus and colonic sphincter open is still uncertain. The pylorus does not open at the end of every peristaltic movement and allow the cud to pass into the duodenum. The normal spasm of the pylorus continues until a certain set of undiscovered conditions are met. These conditions may yet be discovered. In the disease known as "spasm of the pylorus" the pylorus never opens. The colonic sphincter remains closed as long as the antiperistalsis of the cecum continues. In all probability this antiperistalsis is timed by the pylorus through the "musculo-neural ligament." The three inches or less of the transverse colon that are connected with the cecum are strongly muscular, and usually contain the dehydrated portions of the cecal contents. At intervals these masses, which have the consistency of soft clay, pass through the colonic sphincter in larger or smaller pencils into the distal colon and are hurried on by the regular peristalsis of this gut to the sigmoid. In ideal health the sigmoid empties itself completely once a day, generally immediately after the morning meal. The consistency of the stool is such that it maintains its form on passage. It weighs about fifty grams but may be three times as much, depending somewhat upon the indigestible residue. On a starvation diet it may fall to twenty grams. More than one-third of the stool is composed of micro-organisms, most of which are dead.

When the test meal begins to pass the pylorus it can be observed in its rapid course to the cecum. It is so much scattered in the twenty-two feet of ileum that it is observed as spotty masses, but the head of the meal can easily be seen to enter the cecum. However, it accumulates rapidly there and before the end of the first seance of twenty minutes a large fraction can be seen piling up in the cecal end of the proximal colon and already beginning to submit to the churning of the antiperistalsis of this viscus. The tail of the test meal reaches the cecum as early as the second (six hour) seance. Generally the stomach and small intestine are entirely free from any barium four hours after the meal is taken. Indeed, it is hardly fair to rate the motor efficiency of the upper intestinal tract normal if it contains barium four hours after ingestion.

Not forgetting the gastric, billiary, pancreatic, and ileal activities so powerful, so subtle, and so fascinating, let us consider for a moment the fate of the residue that is passed through the ileocecal sphincter into the cecum during the four hours after each meal. Unfortunately it is not possible to determine just what conditions are found after the normal meal in the normal individual. It is safe, however, and accurate enough for our purpose, to say that nearly a quart of semi-liquid material, containing seeds, cellulose, and other indigestible residue enters the cecum after each meal and even in starvation a smaller portion of intestinal residue constantly enters the cecum. The cecum, like the stomach, is very active. It is always in more or less rapid and violent motion. The antiperistaltic waves of the proximal colon begin at the colonic sphincter, while at the same moment peristaltic waves pass along the transverse colon to the left. In a patient with carcinoma of the descending colon I recently observed the exaggerated antiperistalsis and peristalsis advancing from the gall-bladder region. It raised the cecum into an egg-shaped tumor on the right and coincidently the descending colon bulged into a less prominent tumor on the left of the abdomen. At the autopsy *in vivo* a few hours later the phenomena were again observed with the cecum and colon in full view. The wall of the hepatic colon and especially the wall of the cecum were greatly hypertrophied and, of course, they were somewhat edematous as compared with the colon below the annular carcinoma. Personally I have never fluoroscopically observed coincident peristalsis and antiperistalsis going out from the colonic sphincter, but other observers have done so repeatedly. The function of this activity in the cecum seems to be the promotion of absorption and dehydration of the residue. Absorption is rapid in the cecum, but slow or nil in the distal colon and rectum. In cases of poisoning, such as mercuric chlorid poisoning, the cecum shows more corrosive action than the stomach itself, while the small intestine and distal colon show no corrosion at all. The residues of gastric, pancreatic, hepatic and intestinal digestion are poured into the cecum to be dehydrated and then passed in a clay-like consistency into the distal colon.

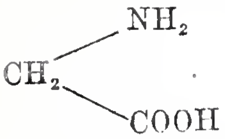
By fluoroscopic examination it has been shown that in health the head of the test meal begins to enter the distal colon quite dehydrated two hours after its ingestion and that eight hours after the meal is taken the tail of the meal has passed the colonic sphincter and the cecum is practically empty. This amounts to an average cecal stay for the barium meal of little more than two hours. The cecum is always receiving some intestinal residue even in starvation. It is certainly not a condition of perfect health if the tail of the meal has not passed the colonic sphincter at the twelve-hour seance.

Food undergoes little or no bacterial action in the normal stomach and the normal small intestine. The gastric juices are distinctly germicidal. The rapid progress of food through the small intestine gives little time for putrefaction. Direct examination has shown that the contents of the small intestine are almost completely sterile.

The great processes of digestion are practically completed when the residue is poured into the cecum for final dehydration. In this cecal residue are the remnants of the digestive and assimilative processes and the incompletely catabolized moiety of the ingested food which has not been absorbed and utilized. Little or no protein is found in this cecal residue.

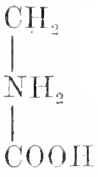
We are particularly interested in the unabsorbed remnants of protein metabolism in the form of amino acids. These simple molecules are the parts of the complex protein molecules which are taken into the body as food and after digestion again assembled in the organism for repair, for energy, and for growth. Not every trace of these amino acids is taken up in the small intestine. Some small portions escape with the detritus into the cecum, and these play a major part in the amine toxaemias.

The amino acids are simple organic acids in which one hydrogen atom is replaced by the amino group NH_2; or otherwise they may be considered as a substituted ammonia, in which one hydrogen of ammonia (NH_3) is replaced by an organic acid. Glycocoll or glycin, amino-acetic acid,



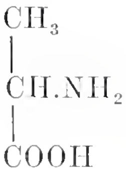
is one of the simplest and first discovered amino acids and illustrates the definition. All amino acids are dialyzable and respond to the ninhydrin test. They are nutrient to bacteria, especially to those of the colon group. The resulting bases are often toxic and it is this toxicity to which attention is here directed.

The various proteins in the food upon catabolism in the intestinal digestion furnish different amino acids. Alanin or alpha-amino-propionic acid; valin, alpha-amino-isovalerianic acid; leucin, alpha-amino-propionic acid; tyrosin, beta-para-oxyphenyl-alpha-amino-propionic acid; cystin, di-beta-thio-alpha-amino-propionic acid; lysin, alpha-epsilon-di-amino capionic acid; histidin, beta-imidazol-alpha-amino-propionic acid, prolin, alpha-pyrrolidine-carboxylic acid, and tryptophan, beta-indolpropionic acid are among these simpler amino acids that escape into the cecum. If the structures of these amino acids are studied it will be noticed that they form groups about the simpler forms. Glycocoll, the simplest of them all, by the acquisition of (CH_3) becomes alanin. When phenyl (C_6H_5) is introduced into the alanin molecule, phenylalanin is obtained, and the additional substitution of an (OH) group leads to the production of tyrosin.



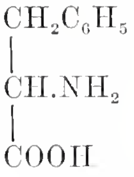
$$\begin{array}{l} CH_2 \\ | \\ NH_2 \\ | \\ COOH \end{array}$$

glycocoll



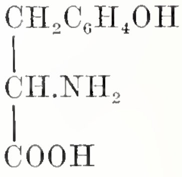
$$\begin{array}{l} CH_3 \\ | \\ CH.NH_2 \\ | \\ COOH \end{array}$$

alanin



$$\begin{array}{l} CH_2C_6H_5 \\ | \\ CH.NH_2 \\ | \\ COOH \end{array}$$

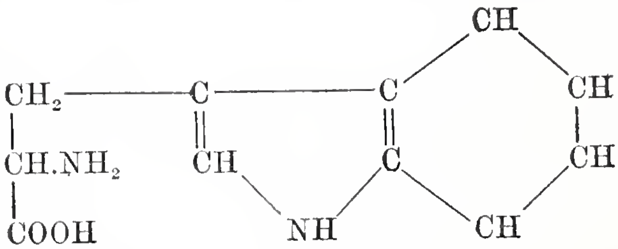
phenylalanin



$$\begin{array}{l} CH_2C_6H_4OH \\ | \\ CH.NH_2 \\ | \\ COOH \end{array}$$

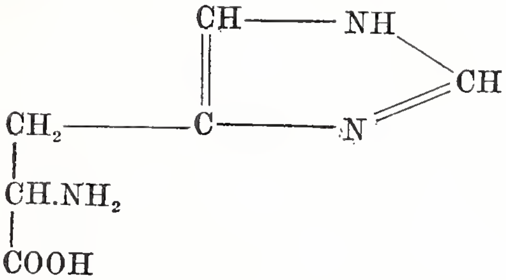
tyrosin

The introduction of the indol group leads to the production of tryptophan,



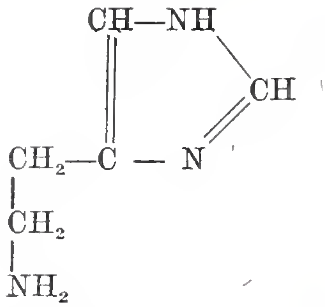
and in the same way the introduction of the iminazol group leads to the formation of histidin.

It happens that the colon bacilli are able to grow on a nutrient material containing the amino acids with the production of the toxic bases. Ergot contains these bases in great profusion, more than twelve have been recognized in ergot and studied. The "pressor" action of ergot is found to be due to the action of one of them, ergotoxin, while the action of ergot upon the uterus is due to another, histamin. These two toxic bases found in ergot result also from the growth of bacilli of the colon group on nutrient media containing tyrosin for the former and histidin for the latter. The firm of Hoffmann La Roche & Co. prepare histamin from the growth of colon bacilli on a nutrient media containing histidin derived from blood, and sell it for hypodermic use in place of ergot. It is put up in ampules containing 1 mg. in 1 c.c. of water and it is termed in the trade "Imido Roche." Its action upon the uterus is equal to a full dose of ergot and there is no local inflammation from the injection. Its chemical name is betaiminazolylethylamine and it is one of the most toxic substances known.



The three best known toxic amines are derived from the three amino acids, tyrosin, tryptophan and histidin by the growth of bacilli, at a temperature of 37° C., of the colon group. These three amino acids are constantly poured into the cecum after each meal and doubtless toxic amines are produced there by the ever present colon bacilli, even in normal individuals. When these and other toxic amines are absorbed into the circulation they are probably catabolized in the liver. Indolethylamine which is derived from tryptohan is certainly thus excreted as indolacetic acid or as indican. Unfortunately histamin which is derived from histidin has not been recognized in the urine in its catabolized form which we might suspect was betaiminazolylacetic acid or as urocanic acid. The fact that urocanic acid was first found in the urine of dogs and the further fact that histamin is tolerated by dogs in enormous doses might lead one to look for an unusual power in these animals to catabolize the venomous betaiminazolylethylamine. Dogs serum should be used in the study of this toxin just as Eustis used the liver of the vulture.

The production of hystamin from histidin is a decarboxylizing process. (COO) is removed. In the method of Hoffman La Roche Co., D. R. Patent 266,522, the process is completed at the end of four hours.



In dementia precox patients we found the blood-pressure low and the injection of adrenalin (Parke, Davis & Co., 0.5, 1:1000 sol.) caused it to fall lower. We found the toxic betaiminazolylethylamine in the stool in large quantities and Ross had already found increased excretion of indolacetic acid in the urine of dementia precox patients. In chronic ergot poisoning mental disturbances resembling dementia precox are observed in more than one-fourth of the afflicted.

It appears, therefore, that while our thesis, namely, that dementia precox is due to a betaiminazolylethylamine intoxication or an intoxication with similarly produced proteogenetic toxic amines, is not substantiated by all the evidence desirable, it indicates with sufficient certainty a suggestion for rational treatment.